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Effects of histamine receptor blockade on cardiovascular changes induced by 35 GHz radio frequency radiation heating

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Summary

1 The role of histamine in heat-induced cardiovascular changes is uncertain. The purpose of this study was to examine effects of histamine H-1- and H-2-antagonism on heart rate, mean arterial blood pressure (MAP), localized body temperature changes, survival times, and lethal body temperatures that occur during the exposure of anaesthetized rats to 35 GHz radio frequency radiation (RFR).

2 Forty-eight ketamine-anaesthetized Sprague–Dawley rats were exposed, in several different treatment groups ($n = 8$ in each), to 35 GHz RFR at a level that resulted in significant body heating and subsequent death. During irradiation, a continuous increase in heart rate and a biphasic response in blood pressure (initial increase followed by a decrease) were observed in all groups of animals.

3 An H-1-antagonist, diphenhydramine (1 mg kg ^{1} body wt) and an H-2-antagonist, cimetidine (5 mg kg ^{1}), administered after sustained RFR exposure, failed to reverse the RFR-induced hypotension. High doses of the drugs (5 and 10 mg kg ^{1}, respectively) also did not alter the response. Post-RFR survival time was significantly decreased in the high-dose drug-treated group, compared with vehicle-treated (0.9% NaCl, 50% ethanol and 50% D5W) controls.

4 In experiments in which the two drugs were administered prior to RFR exposure, MAP in animals receiving high-dose antihistamines was significantly depressed compared with that of vehicle-treated animals during the first 35 min of RFR exposure. Antihistamine pretreatment, however, did not alter the total RFR exposure time required for death to occur.

5 In summary, pharmacological blockade of H-1 and H-2 receptors is not beneficial in anaesthetized rats made hypotensive by RFR exposure. This indicates that activation of H-1 and H-2 receptors by histamine does not occur to any significant extent and does not mediate the hypotensive response developed in this model of hyperthermia.

Keywords: histamine, H_2 receptors, H_1 receptors, radio frequency radiation, blood pressure, heart rate

Introduction

The increased use of radio frequency radiation (RFR) exposure sources capable of generating millimetre wavelengths for military and civilian purposes (e.g. communications, radar imaging/mapping, space power beaming, radiometry) will continue to generate interest in possible biological effects of exposure to these sources. Among the potential effects, an increase in body temperature is the primary consequence of whole body exposure to high levels of RFR. The use of RFR to study physiological changes during heat stress has been discussed previously (e.g. Jauchem & Frei, 1994).

Cardiovascular responses due to RFR induced heating are, in general, similar to responses to environmental heating as described by Kregel & Gisolfi (1990). Exposure to short wavelength RFR (including millimetre waves), however, can result in energy deposition at the body surface without deposition at deeper sites. Thus, there will be differences in temperature gradients within the

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body resulting from short wavelength RFR *vs.* environmental heating. These differences may, in turn, lead to quantitative variations in the magni tude of cardiovascular changes (Jauchem & Frei, 1992). In addition, extended RFR exposure of this type will result in increased core body temperature due to circulatory transfer of heat. Ryan, D'Andrea, Jauchem & Mason (2000) have reviewed the topic of millimetre wave heating.

Frei, Ryan, Berger & Jauchem (1995) previously demonstrated that sustained whole body exposure to RFR energy of approximately millimetre wave length (35 GHz) produces shock like hypotension in anaesthetized Sprague Dawley rats. In these studies, circulatory collapse occurred when skin temperature was rapidly elevated to levels much greater than those measured at deeper sites within the body. Heart rate (HR) and mean arterial blood pressure (MAP) changes were similar to those that occur during environmental heat stress. It should be noted, however, that circulatory collapse occurred at much lower core temperatures than observed in heatstroke models of environmental heating (Kregel & Gisolfi, 1990; Frei *et al.*, 1995).

Histamine is a potent vasodilator that has been implicated as a mediator in several different forms of shock. Previous studies (the majority listed here using the Sprague Dawley rat) have elucidated the role of histamine in cardiovascular changes occur ring during such insults as endotoxaemia (Brackett, Schaefer & Wilson, 1985), hepatic inflow occlu sion (Kogure & Suzuki, 1992), haemorrhagic shock (Johnson, Charya, Atkins, Wiesmann & Pearce, 1997), mesenteric ischaemia (Kaszaki, Boros, Szabó & Nagy, 1994), anaphylactic shock (Mink *et al.*, 1999), and polyamine induced shock (Figueroa, Stone, Cohly, Lehan & Markov, 2001). The role of histamine in heat induced hypotension, however, is not clear.

Histamine is produced in and released from mast cells, which are found in large numbers in the skin of Sprague Dawley rats (Shakhanbeh & Abo Galyon, 1996). A variety of noxious stimuli can cause skin mast cells to release histamine. Sub stance P, a neuropeptide present in C fibres of the skin, can mediate such release (Dunnick, Gibran & Heimbach, 1996). In addition, histamine immu noreactive nerves have been identified in the skin of Sprague Dawley rats (Johansson, Virtanen & Hilliges, 1995). Thermal injury can cause release of histamine from the skin (Ward & Till, 1990). Serum histamine is significantly higher in rats with superficial dermal burns than in those with deep burns (Shimizu *et al.*, 2002).

Exposure to RFR at relatively lower wavelengths (2450 MHz) results in disruption of mast cells in the peritoneal fluid of rats (Valtonen, 1966). Because of the high skin temperatures reached during 35 GHz RFR exposure, it is plausible such exposure could disrupt skin mast cells. Subsequent release of histamine may play a role in producing the circulatory failure that results.

In support of this hypothesis, Sharma & Cervos Navarro (1991) reported a beneficial effect of H 2 receptor antagonism by cimetidine during heat stress (caused by environmental heating) in rats. In addition, cimetidine can prevent harmful sequelae caused by scald injury to skin in rodents (Boykin, Eriksson, Sholley & Pittman, 1980). Pretreatment with a combination of an H 1 and H 2 antagonist attenuates harmful events (such as microvascular leakage) caused by injury in rodent skin (He & Walls, 1997).

The purpose of the current experiments was to examine the effects of combined H 1 and H 2 receptor blockade, with diphenhydramine and cimetidine, respectively, on responses to heating of anaesthetized Sprague Dawley rats with 35 GHz RFR. HR, MAP, localized body temperature chan ges, survival times, and lethal body temperatures were measured.

Methods

Animal care

All experiments and animal care procedures were approved by the Institutional Animal Care and Use Committee of the Air Force Research Laboratory, Brooks City Base, TX, and were conducted accord ing to the 'Guide for the Care and Use of Laboratory Animals' prepared by the Institute of Laboratory Animal Resources National Research Council.

Male Sprague Dawley rats (total $n = 48$) were obtained from the colonies of Charles River (Wilmington, MA). They were individually housed in standard plastic cages ($26 \times 23 \times 20.5$) with water and food available *ad libitum*. Rats weighed between 350 and 400 g at the time of the experi ments. A 12:12 h light dark cycle (light on at 06.00) was used, and the room temperature was maintained at 22 24 °C.

Instrumentation and preparation

Ketamine HCl (Ketalar; Parke Davis, Morris Plains, NJ, USA; 150 mg kg^{-1}, intramuscularly) was administered, with supplemental doses provi ded as necessary during experimentation. Ketamine administration at this dose level has been shown to produce prolonged surgical anaesthesia in Spra gue Dawley rats (Smith, Pekoe, Martin & Coalgate, 1980; Frei & Jauchem, 1989; Jauchem & Frei, 1994), and results in a stable animal preparation compatible with physiological moni toring (Jauchem & Frei, 1991). Ketamine exerts minimal effects on temperature regulation in rats (Refinetti & Carlisle, 1989), and is known for its lack of significant autonomic, cardiovascular, or

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respiratory effects in this animal model. Although some anaesthetics, such as enflurane and pento barbital, can affect brain histaminergic systems (which are involved in blood pressure and body temperature regulation), ketamine is ineffective in this respect in rodents (Baba, Nishibori, Oishi, Saeki & Kosaka, 1987).

Colonic temperature (T_c) was maintained at 37.0 ± 0.5 °C during all surgical procedures. A Teflon catheter (PE 50) was placed into the right jugular vein for drug administration. Additionally, the left carotid artery was instrumented with a Teflon catheter (PE 50) for measurement of arterial blood pressure and collection of arterial blood. The catheter was attached to a precalibrated blood pressure transducer (Century, Model CP 01, Ingle wood, CA, USA). A lead II ECG was obtained by use of nylon covered fluorocarbon leads attached to a shielded cable placed outside the radio frequency field. All measured variables were recor ded continuously throughout experimentation on a Gould TA2000 recorder (Gould Inc., Cleveland, OH, USA).

Animals were also instrumented to monitor temperature at five sites: (i) left subcutaneous (lateral, mid thoracic, side facing the RFR ant enna); (ii) right subcutaneous (lateral, mid thor acic, side facing away from the RFR source); (iii) right tympanic; (iv) colonic (5 6 cm post anus); and (v) tail (subcutaneous, dorsal, 1 cm from base). The tail was placed within a 4 cm diameter tube wrapped with two layers of RFR shielding material (Bekaert Steel Wire Corp., Dyersburg, TN, USA). Thus, the tail was shielded from direct exposure to RFR and yet air was allowed to flow freely around it. All temperature measurements were obtained via thermistor probes (BSD Medical Corporation, Salt Lake City, UT, USA) attached to a precision thermometry system (BSD Medical Corporation, Model BSD 200). All temperature and cardiovas cular data were A/D (analogue to digital) converted by an IBM compatible custom designed Physiolo gical Monitoring System (Berger, Frei & Jauchem, 1991) with real time graphics display and data analysis capabilities.

RFR equipment

Continuous wave 35 GHz fields were generated by a Millimeter Wave Exposure System (Applied Electromagnetics, Inc., Atlanta, GA, USA). Irradi ation was conducted under far field conditions with the animal centred along the boresight, 110 cm from the antenna. The incident power density of the field was determined at the exposure site with an electromagnetic radiation monitor (Narda Microwave Corporation, Hauppauge, NY, USA). The generator power output was monitored throughout exposure with a Model 4 32 B Hewlett Packard powermeter. Irradiation was conducted in an Eccosorb RF shielded anechoic chamber at the Radio Frequency Radi ation Branch of the Air Force Research Laborat ory, Brooks City Base, TX. Chamber temperature and relative humidity were maintained at 27.0 ± 0.5 °C and 20 ± 5%, respectively, during experimentation.

Drugs

Diphenhydramine was solubilized in 0.9% NaCl immediately prior to administration. Cimetidine was solubilized in 50% ethanol and 50% D5W prior to injection.

Experimental procedure

After surgery, the rat was placed on a Plexiglas® holder in the anechoic chamber (Frei *et al.*, 1995). The animal was then instrumented with tempera ture probes and cardiovascular leads for data collection. During a 5 min control period, baseline temperatures were recorded and T_c was maintained between 37.0 ± 0.5 °C using a water perfused heating pad. After the control period, the animal was exposed in the H orientation (left lateral exposure, long axis of body parallel to electric field) to 35 GHz RFR at an incident power density of 75 mW cm^{-2}. This power density will result in a whole body specific absorption rate of approxi mately 13 W kg^{-1} in rats of the size used in this study (Frei *et al.*, 1995). Cardiovascular and tem perature parameters were continuously recorded during the control period, throughout the RFR exposure, and following exposure.

Protocol 1. In this protocol, we determined whe ther combined pharmacological blockade of H 1 and H 2 receptors could reverse the hypotension induced by sustained RFR exposure and, conse quently, increase survival time following RFR exposure. After a 5 min control period, the rats were exposed to RFR until MAP decreased to 75 mmHg. Previous experiments indicated that, if irradiation is discontinued at this point, MAP will continue to decline until death (Ryan, Frei, Berger & Jauchem, 1996; Jauchem, Ryan, Lovelace & Frei, 1997; Ryan, Frei & Jauchem, 1997). We therefore discontinued RFR exposure at this point and arbitrarily defined this as the point of circulatory shock induction. Immediately after the cessation of RFR exposure, the H 1 and H 2 receptor antagonists diphenhydramine and cimeti dine, respectively, were administered intravenously in a single bolus injection. Group 1 ($n = 8$) received a low dose of both diphenhydramine (1 mg kg^{-1}) and cimetidine (5 mg kg^{-1}). Group 2 ($n = 8$) received a higher dose of both diphenhydr amine (5 mg kg^{-1}) and cimetidine (10 mg kg^{-1}). Group 3 ($n = 8$) received a bolus injection

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consisting of both vehicles. Each vehicle was administered in a volume equivalent to that used for drug dilution. Each rat received only one dose of either the drugs or the vehicle. Following administration of the drug or the vehicle, the rat was monitored until death.

Protocol 2. To determine whether pretreatment with H 1 and H 2 receptor antagonists could alter the onset of circulatory shock induction, animals in this protocol received diphenhydramine and cimetidine before initiation of RFR exposure. Each animal was first placed on the Plexiglas® holder in the exposure chamber and monitored for a 5 min control period. Following this, diph enhydramine and cimetidine were administered intravenously in a manner identical to that in protocol 1. Group 4 ($n = 8$) received the low doses of diphenhydramine (1 mg kg^{-1}) and cimetidine (5 mg kg^{-1}), while group 5 ($n = 8$) received the higher doses of diphenhydramine (5 mg kg^{-1}) and cimetidine (10 mg kg^{-1}). Group 6 ($n = 8$) received vehicles. Ten minutes following the injection, RFR exposure was initiated and was continued until death.

Data analysis

Data from this study are presented as mean ± SEM. The time of exposure to RFR necessary to reach the chosen endpoint (i.e. MAP = 75 mmHg) in proto col 1 varied across individual animals (46.9 ± 1.7 min). Cardiovascular and thermal data were therefore normalized for percentage of time to endpoint in order to make valid comparisons among animals with varying durations of RFR exposure. To determine differences between vehicle *vs*. histamine receptor antagonist treated groups, a two way analysis of variance (ANOVA) with repea ted measures followed by the Student Newman Keuls (SNK) multiple comparison test was performed on the normalized data (related to amount of change from time '0' baseline).

Cardiovascular and thermal data from protocol 2 are presented in absolute time intervals of 2.5 min. To determine the differences among groups, a two way ANOVA with repeated measures was applied, followed by the SNK.

For protocols 1 and 2, temperatures at each measured site before and at cessation of RFR exposure were compared using a two way ANOVA, followed by the SNK when necessary.

Results

Protocol 1: RFR exposure until MAP of 75 mmHg followed by antihistamines

Temperatures at different sites before and at the end of RFR exposure are listed in Table 1. All postexposure temperatures were significantly hig her than pre exposure values. Only one significant difference was found between the different treat ment groups: postexposure tail temperature was higher in the low dose drug treated animals than in the vehicle treated group.

The time courses of left subcutaneous and colonic temperatures, and of MAP and HR are shown in Figs 1 & 2, respectively. (In the high dose group, animals survived only long enough for one measurement after cessation of RFR exposure.) For each parameter, there were sig nificant changes over time in each treatment group. There were, however, no significant differences between changes (from baseline at time zero) between groups. Although initial HR was significantly lower in high dose drug treated animals, the pattern of HR increase was similar in all groups. It is possible, however, that the lower initial HR in that group affected subsequent changes during the experiments. Administration of diphenhydramine and cimetidine (either dose level) following RFR exposure failed to reverse the hyperthermia induced hypotension, as indi cated by a continued decline in MAP after drug administration. Administration of the high doses

Table 1 Colonic (T_c), tympanic (T_{tym}), left (T_{sl}) and right (T_{sr}) subcutaneous, and tail (T_t) temperatures immediately before and at the end of RFR exposure

	T_c (°C)	T_{tym} (°C)	T_{sl} (°C)	T_{sr} (°C)	T_t (°C)
Pre-RFR					
Vehicle	36.9 ± 0.1	36.3 ± 0.2	34.4 ± 0.4	35.7 ± 0.4	27.5 ± 0.3
Low dose	37.1 ± 0.1	37.0 ± 0.1	34.3 ± 0.3	35.1 ± 0.5	29.1 ± 0.3
High dose	37.1 ± 0.1	37.0 ± 0.1	34.4 ± 0.4	35.7 ± 0.2	28.9 ± 0.4
Post-RFR					
Vehicle	41.9 ± 0.3	40.9 ± 0.3	48.6 ± 0.5	38.6 ± 0.7	31.4 ± 0.7
Low dose	41.4 ± 0.4	40.6 ± 0.6	48.9 ± 0.2	37.2 ± 0.9	33.6 ± 0.6*
High dose	40.8 ± 0.3	40.5 ± 0.2	48.9 ± 0.5	36.9 ± 0.5	32.1 ± 0.5

Rats were treated with diphenhydramine + cimetidine 10 min before RFR exposure. Low dose = 1 mg kg^{-1} diphenhydramine + 5 mg kg^{-1} cimetidine; high dose = 5 mg kg^{-1} diphenhydramine + 10 mg kg^{-1} cimetidine.
*Significantly different from vehicle.

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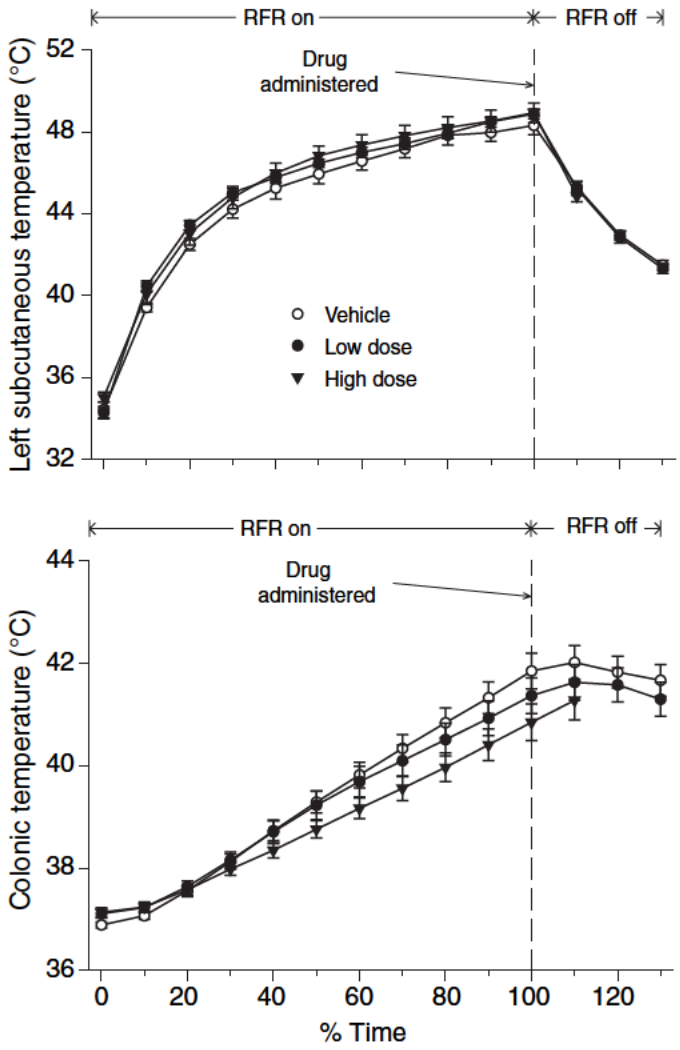

Figure 1 Effects of combined administration (following RFR exposure until MAP dropped to 75 mmHg) of diphenhydramine and cimetidine on left subcutaneous and colonic temperatures. 'Low dose' = 1 mg kg ^{1} diphenhydramine and 5 mg kg ^{1} cimetidine. 'High dose' = 5 mg kg ^{1} diphenhydramine and 10 mg kg ^{1} cimetidine. In each group, $n = 8$. Time is represented as a percentage of the total RFR exposure time to account for differences in duration of individual experiments.

of antihistamines significantly decreased the post RFR survival time, compared with vehicle treated controls (Fig. 3).

Protocol 2: Pretreatment with antihistamines followed by RFR exposure until death

Temperatures at different sites before and at the end of RFR exposure are listed in Table 2. All temperatures at death were significantly higher than predrug and pre RFR values. There were no significant differences, however, between the dif ferent treatment groups. Thus, pretreatment with diphenhydramine and cimetidine did not signifi cantly alter either control temperatures or temper atures at the end of RFR exposure.

The time courses of left subcutaneous and colonic temperatures, and of MAP and HR are shown in Figs 4 & 5, respectively. For each parameter, there were significant changes over time in each treatment group. Pretreatment with the antihistamines produced a decrease in MAP before RFR exposure began (Fig. 5). The change in MAP from time '0' baseline in animals receiving antihistamines at the higher doses remained significantly depressed compared with that of vehicle treated animals during the first 35 min of RFR exposure. Antihistamine pretreat ment did not alter the total RFR exposure time required for death to occur (vehicle 59.8 ± 2.2 min, low dose 60.0 ± 1.3 min, high dose 63.0 ± 3.7 min).

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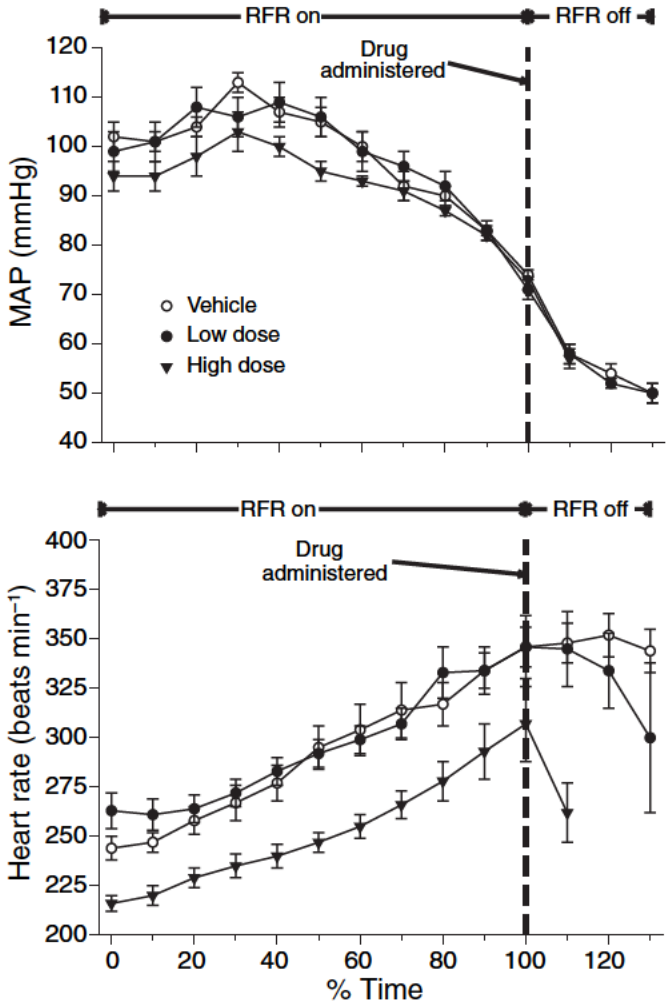

Figure 2 Effects of combined administration (following RFR exposure until MAP dropped to 75 mmHg) of diphenhydramine and cimetidine on mean arterial pressure (MAP) and heart rate. 'Low dose' = 1 mg kg ^{1} diphenhydramine and 5 mg kg ^{1} cimetidine. 'High dose' = 5 mg kg ^{1} diphenhydramine and 10 mg kg ^{1} cimetidine. In each group, $n = 8$. Time is represented as a percentage of the total RFR exposure time to account for differences in duration of individual experiments.

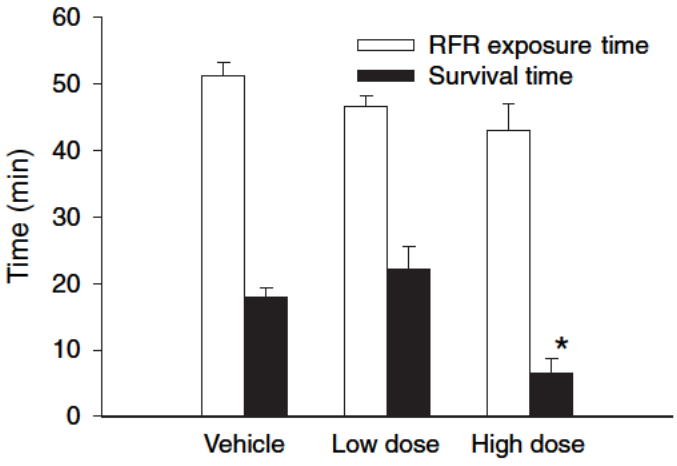

Figure 3 Effects of combined administration (following RFR exposure until MAP dropped to 75 mmHg) of diphenhydramine and cimetidine on RFR exposure time (i.e. time from beginning of exposure and drug until mean arterial pressure decreased to 75 mm Hg) and subsequent survival time. 'Low dose' = 1 mg kg ^{1} diphenhydramine and 5 mg kg ^{1} cimetidine. 'High dose' = 5 mg kg ^{1} diphenhydramine and 10 mg kg ^{1} cimetidine. In each group, $n = 8$. *Significantly different from vehicle.

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Table 2 Colonic (T_c), tympanic (T_{tym}), left (T_{sl}) and right (T_{sr}) subcutaneous, and tail (T_t) temperatures immediately before drug infusion and RFR exposure, and at death

	T_c (°C)	T_{tym} (°C)	T_{sl} (°C)	T_{sr} (°C)	T_t (°C)
Pre-drug					
Vehicle	37.0 ± 0.1	36.5 ± 0.1	34.0 ± 0.5	34.0 ± 0.5	27.9 ± 0.4
Low dose	37.2 ± 0.0	37.0 ± 0.1	34.6 ± 0.3	35.2 ± 0.6	28.8 ± 0.7
High dose	37.0 ± 0.1	36.7 ± 0.1	35.0 ± 0.4	35.0 ± 0.5	28.6 ± 0.3
Pre-RFR					
Vehicle	36.8 ± 0.1	36.3 ± 0.1	34.4 ± 0.6	33.7 ± 0.5	27.7 ± 0.2
Low dose	36.9 ± 0.1	36.6 ± 0.1	34.6 ± 0.3	34.6 ± 0.5	28.6 ± 0.5
High dose	36.5 ± 0.1	36.1 ± 0.1	33.7 ± 0.4	33.8 ± 0.6	29.8 ± 0.5
At death					
Vehicle	42.5 ± 0.3	41.5 ± 0.3	49.7 ± 0.6	36.7 ± 1.1	32.5 ± 0.8
Low dose	41.7 ± 0.2	40.9 ± 0.4	50.0 ± 0.3	36.6 ± 1.8	30.9 ± 0.3
High dose	42.5 ± 0.6	41.4 ± 0.4	48.4 ± 1.1	36.8 ± 1.8	32.2 ± 1.3

Rats were treated with diphenhydramine + cimetidine 10 min before RFR exposure. Low dose = 1 mg kg ^{1} diphenhydramine + 5 mg kg ^{1} cimetidine; high dose = 5 mg kg ^{1} diphenhydramine + 10 mg kg ^{1} cimetidine.

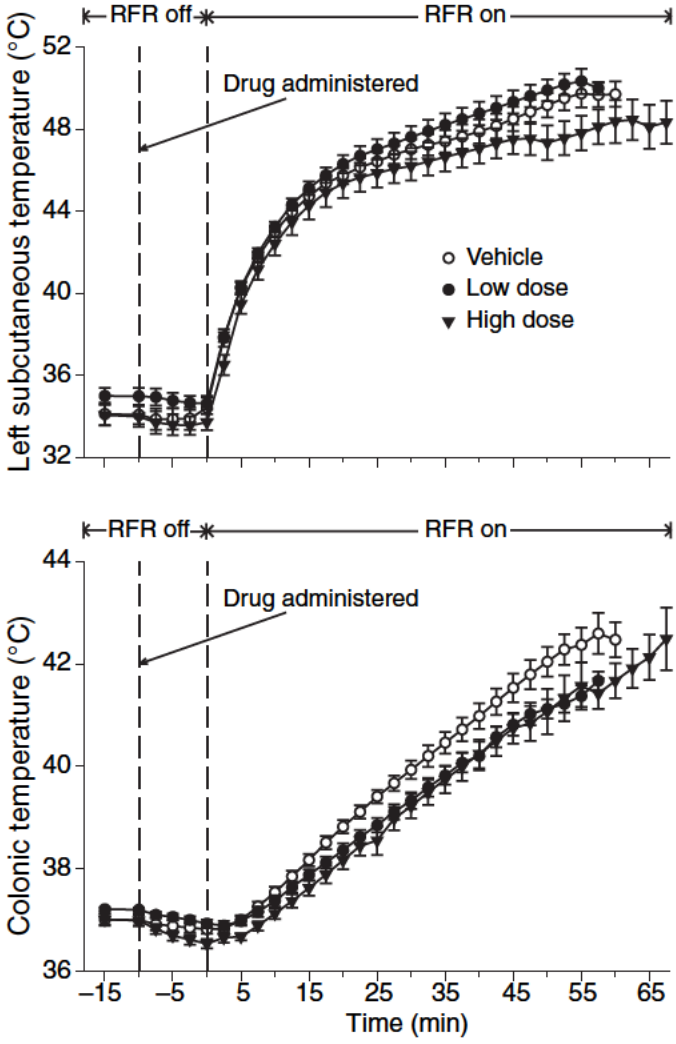

Figure 4 Effects of combined administration of diphenhydramine and cimetidine, followed by RFR exposure, on left subcutaneous and colonic temperatures. 'Low dose' = 1 mg kg ^{1} diphenhydramine and 5 mg kg ^{1} cimetidine. 'High dose' = 5 mg kg ^{1} diphenhydramine and 10 mg kg ^{1} cimetidine. In each group, $n = 8$.

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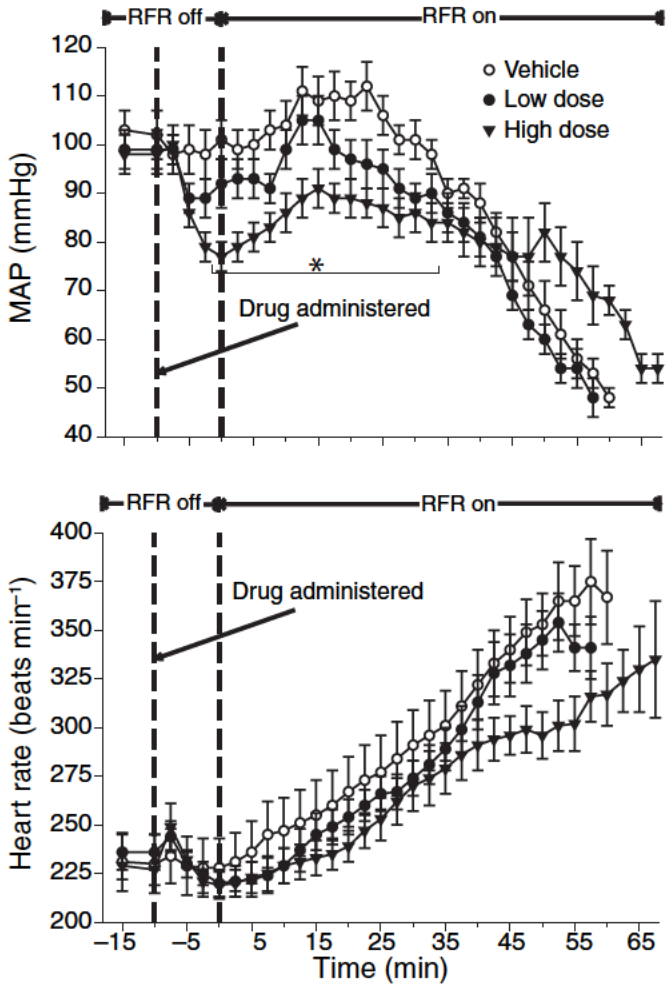

Figure 5 Effects of combined administration of diphenhydramine and cimetidine, followed by RFR exposure, on mean arterial pressure (MAP) and heart rate. 'Low dose' = 1 mg kg ^{1} diphenhydramine and 5 mg kg ^{1} cimetidine. 'High dose' = 5 mg kg ^{1} diphenhydramine and 10 mg kg ^{1} cimetidine. In each group, $n = 8$. *Significant difference between high dose and vehicle.

Discussion

Overall pattern of HR and MAP changes during RFR exposure and heating

The biphasic change (initial increase followed by decrease) in MAP, and the gradual rise in HR throughout the exposure period, were similar to changes previously found by other investigators during experiments of lethal environmental heat stress in anaesthetized rats (Kielblock, Strydom, Burger, Pretorious & Manjoo, 1982; Kregel & Gisolfi, 1990). In earlier studies of terminal exposures of anaesthetized rats to 2.45 GHz (Jau chem & Frei, 1994; Jauchem, Frei, Chang & Berger, 1995; Jauchem, Chang & Frei, 1996), 2.8 GHz (Jauchem, Frei & Heinmets, 1984), and 5.6 GHz RFR (Jauchem, Frei & Heinmets, 1983, 1988), the pattern of HR and MAP changes was also qualitatively comparable.

The pattern of HR and MAP changes during hyperthermia could be the result of diminished venous return as a result of massive venodilation, which could cause decreased stroke volume with a subsequent drop in cardiac output. Miki, Morimoto, Nose, Itoh & Yamada (1983) observed a prominent reduction in central venous pressure during severe hyperthermia. The mecha nisms controlling such a decrease in pressure during heat stress are unclear. This diminished venous pressure, along with an accompanying decrease in cardiac filling, may be the limiting factor in survival during heat stress. Kregel & Gisolfi (1990) suggested that heating could prevent vasomotor stimuli from exerting an effect on the contractile apparatus of blood vessels. Takamata, Nose, Mack & Morimoto (1990) also suggested that the sudden decrease in MAP during hyperthermia may be due to a dysfunction in the peripheral circulation and a reduction in

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venous return. Previously, Morimoto & Nose (1984) reported that vascular compliance is lower during hyperthermia.

A paradoxical bradycardia can develop in severe hypotensive hypovolaemic shock (Secher, Jensen, Werner, Warberg & Bie, 1984). In contrast to this, in experiments dealing with terminal heat stress, whether due to environmental exposure (Kielblock *et al.*, 1982; Kregel & Gisolfi, 1990) or RFR (as in the present experiments), tachycardia continued until death.

Effects of antihistamines

As the tail was shielded from direct exposure to RFR, any increase in tail temperature would be likely to be related to circulatory transfer of heat. During environmental heating, diversion of blood to the tail occurs with an increase in body temperature (Grant, 1963). The surface area to volume relationship of the tail allows for rapid dissipation of heat into the environment. Histamine induced relaxation of isolated rat tail arteries (synonymous with vasodilation) involves an endothelium independent mechanism that is sensitive to cimetidine (Grifoni & Brendhack, 2000). In our current study, postexposure tail temperature was elevated in the low dose (administered following RFR exposure) drug treated animals, compared with the vehicle treated group. Such an increase in temperature could be related to vasodilation in the tail. It is not known, however, why high dose antihistamine treated animals did not show an increase in tail temperature.

The actions of H 1 and H 2 antagonists on body temperature changes are dependent on the route of administration (Dey & Mukhopadhaya, 1986). Cimetidine injection can inhibit hypothermia in rats (Brus, Krzeminski, Juraszczyk, Kurcok & Felinska, 1985). Conversely, chronic administration of diphenhydramine has been shown to block hyperthermia in rats (Nath, Patnaik, Saxena & Gupta, 1997). Dhawan, Shukla & Srimal (1982) presented a more complicated picture of effects of histamine on body temperature, with low and high doses of histamine causing hypothermia and hyperthermia, respectively. They concluded that H 1 receptors mediate hypothermia, while H 2 receptors mediate hyperthermia. Nowak (1982), however, reported that cimetidine, although blocking the hypothermic action of an H 2 agonist, had no effect on body temperature when administered alone. Although there were no significant differences in temperatures at death between groups in the present study, post RFR survival time was significantly decreased in the high dose (administered following RFR exposure) antihistamine group. This effect was unexpected. In fact, Brackett *et al.* (1985) found that combined treatment with both diphenhydramine and cimetidine resulted in increased survival time during endotoxin induced shock.

In our experiments, the decrease in MAP in animals after pretreatment with antihistamines was consistent with findings by Paakkari, Totterman, Kupari, Karppanen & Paakkari (1982). Those investigators reported that i.v. cimetidine induced hypotension in anaesthetized rats; diphenhydramine pretreatment did not antagonize the hypotensive effect. It should be noted that the doses of antihistamines used in our experiments were similar to those in previous studies of diphenhydramine (e.g. Dimlich, 1985; Ulloa & Zaninovich, 1986; Carceller *et al.*, 1994; Wan, Wetmore, Sorensen, Greenberg & Nance, 1994) and cimetidine (e.g. Ezeamuzie, Nwankwoala & Emenike, 1986; Ulloa & Zaninovich, 1986; Couture, Gupta, Kérouac & Regoli, 1987) administered intravenously to rats by other investigators.

Other investigators have suggested several potential mechanisms of hypotensive effects of both H 1 and H 2 antagonists. In rats, H 1 antagonism can attenuate histamine induced release of noradrenaline (Bealer, 1993) or arginine vasopressin (Knigge, Willems, Kjaer, Jørgensen & Warberg, 1999). As noradrenaline and arginine vasopressin could each cause increases in blood pressure, inhibition of such release may contribute to hypotension, depending on interaction of other factors. In addition, humans with certain conditions react to administration of H 1 receptor antagonists with severe hypotension that is reversible by i.v. adrenaline (Roberts, Turk & Oates, 1982). Regarding H 2 antagonism, one potential mechanism of the hypotensive action of i.v. cimetidine is vasodilation (with a corresponding decrease in peripheral resistance), in both rats (Paakkari *et al.*, 1982) and humans (Totterman, Kupari, Paakkari & Nieminen, 1985). Due to the complex nature of possible mechanisms and interactions of different substances, it would be difficult to develop a unifying hypothesis for the hypotensive effects of high dose histamine antagonism in the present experiments.

The lack of a beneficial effect of antihistamines in our study is consistent with findings of Johnson *et al.* (1997), who used a different model of cardiovascular collapse: haemorrhagic shock in the Sprague Dawley rat. As in our study, those investigators used diphenhydramine and cimetidine as histamine antagonists. They concluded that histamine is not an important mediator of cardiovascular sequelae seen in the decompensatory phase of shock, although histamine levels rise coincidentally during this phase. The lack of a beneficial effect of antihistamines in our study does negate the possibility of some involvement of histamine in the overall responses. The model of hyperthermia was of a rather severe nature, and partial activation of some histamine receptors could still have occurred.

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Possible role of other endogenous circulating factors during RFR exposure and heating

The role of other endogeneous circulating factors in heat induced circulatory collapse (whether due to environmental or RFR heating) has been studied previously. McMeeken & Bell (1990) reported a pressor effect of RFR exposure and presumed that reflex adrenomedullary activation was involved, as plasma catecholamines were elevated. Gisolfi, Matthes, Kregel & Oppliger (1991) found that changes in sympathetic nerve activity and plasma catecholamines were not associated with mesenteric vasodilation that precedes heatstroke. Ryan, Jauchem, Tehrany & Boyle (2002) previously found that platelet activating factor was not associated with RFR induced circulatory failure. Nitric oxide was not associated with either RFR (Ryan *et al.*, 1996) or environmental heat induced (Ryan, Tehrany & Jauchem, 2001) circulatory collapse. McMeeken & Bell (1990) did not find any evidence that prostaglandins or kinins were involved in vasodilation that occurred during RFR exposure.

A marked increase in plasma levels of vasopres sin occurs during heatstroke after heavy exercise (Aarseth, Eide, Skeie & Thaulow, 1986). In addi tion, circulating angiotensin converting enzyme activities in exertional heatstroke patients on admission were significantly lower than in normal subjects (Shieh, Shiang, Lin, Shiao & Wang, 1995). Effects of non exertional heating on vasopressin and the angiotensin system, however, have not been elucidated. It will be important to study these and other factors in future investigations of envi ronmental and RFR induced heating.

Summary

In summary, pharmacological blockade of H 1 and H 2 receptors is not beneficial in anaesthetized rats made hypotensive by RFR exposure. This indicates that activation of H 1 and H 2 receptors by histamine does not occur to any significant extent and does not mediate the hypotensive response developed in this model of hyperthermia.

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